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Does management of lipid lowering differ between specialists and primary care: Insights from GOAL Canada

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Abstract

Background: We studied whether significant differences in care gaps exist between specialists and primary care physicians (PCPs).

Methods: GOAL Canada enrolled patients with CVD or familial hypercholesterolemia (FH) and LDL-C > 2.0 mmol/L despite maximally tolerated statin therapy. During follow-up, physicians received online reminders of treatment recommendations based on Canadian Guidelines.

Results: A total of 177 physicians (58% PCPs) enrolled 2009 patients; approximately half of the patients were enrolled by each physician group. Patients enrolled by specialists were slightly older (mean age 63 years vs 62), female (45% vs 40%), Caucasian (77% vs 65%), and had a slightly higher systolic pressure and lower heart rate. Patients enrolled by specialists had less frequent history of FH, diabetes, hypertension, chronic kidney disease and liver disease but more frequent history of coronary artery disease, atrial fibrillation and premature family history of CVD. There was no significant baseline difference in LDL-C, HDL-C or non-HDL-C, although total cholesterol and triglycerides were slightly higher in patients managed by PCPs. At baseline, PCPs were more likely to use statins (80% vs 73%, $P = .0002$) and other therapies such as niacin or fibrate (10% vs 6%, $P = .0006$) but similar use of ezetimibe (24% vs 27%, $P = .15$). At the end of follow-up, specialists used less statins (70% vs 77%, $P = .0005$) and other therapies (6% vs 10%, $P = .007$) but more ezetimibe (45% vs 38%, $P = .01$) and the same frequency of PCSK9i (28% vs 27%, $P = .65$). The proportion of patients achieving the recommended LDL-C level of 2.0 mmol/L or below (primary endpoint) was similar at last available visit between specialists and PCPs (44% vs 42%, $P = .32$).

Conclusion: Despite minor differences in the clinical profile of their patients, both PCPs and specialists actively participate in the management of lipid-lowering therapy in high-risk CVD patients and experience similar challenges and care gaps.

1 | INTRODUCTION

Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease (CVD) and many guidelines recommend LDL-C lowering to reduce the risk of both cardiovascular events and mortality in patients with CV disease [1] and familial hypercholesterolemia (FH).

The 2016 Canadian Cardiovascular Society clinical practice guidelines (CPG) recommend initiation of LDL-C lowering with high-intensity statin therapy and the addition of ezetimibe or a

PCSK9i as needed if LDL-C is not lowered by at least 50% or to a level below 2.0 mmol/L in patients with established CVD or FH.[2] Despite specific and updated CPG, many patients fail to reach guideline-recommended levels.[3-10] GOAL Canada[11] reported that physician education based on the reminder system significantly improved care as measured by the proportion of patients achieving the recommended LDL-C level in relation to a greater utilization of recommended[2] lipid-lowering therapies. CPG recommendations do not typically distinguish between the respective roles of primary care physicians (PCPs) or specialists; further, it is not known whether the adoption of guidelines, pattern of management and specific strategies for lowering LDL-C are different for these groups of physicians. This post hoc analysis of GOAL Canada[11] aims to ascertain if any differences exist between PCPs and specialists with respect to the utilization of lipid-lowering therapies which either group of physicians can prescribe.

What's known

- Low-density lipoprotein cholesterol (LDL-C) lowering results in lowering of cardiovascular morbidity and mortality and is recommended as a first line therapy in secondary prevention
- Clinical practice guidelines recommend the use of high intensity statin therapy followed by consideration for addition of ezetimibe and if needed PCSK9 inhibition
- Many patients do not achieve recommended LDL-C level, in part, because of decision not to add additional therapy beyond statin (treatment inertia)

What's new

- This quality improvement initiative found treatment inertia beyond statin therapy to be similar among primary care physicians and specialists

2 | METHODS

The Guidelines Oriented Approach to Lipid lowering (GOAL) Canada[11] was an interventional program supported by Amgen Canada. It was an investigator-initiated study started in 2015 and coordinated by the Canadian Heart Research Centre, an academic research and education physician organization. The intervention studied was physician education/lipid management reminders applied at the end of each of three visits based on data entry in the electronic case report form (eCRF). Participating physicians received fair market value compensation for completing the electronic case report form. The study was approved by central and institutional research ethics boards where appropriate and all enrolled patients provided informed consent.

Invitations to participate were sent to 750 Canadian physicians across Canada from a proprietary (CASL Regulation) Canadian Heart Research Centre list of physicians who participated in prior cholesterol-oriented data collection studies[12,13] and 248 were activated to enrol their patients for whom the participating physicians had the primary role for cholesterol-lowering management. These physicians were asked to consecutively enrol at least 12 of their patients with either (a) clinical vascular disease such as coronary artery disease (CAD), cerebrovascular disease, abdominal aortic aneurysm or peripheral arterial disease; or, (b) FH, as defined in the Canadian guidelines.[2] In addition, all patients had to have an LDL-C >2.0 mmol/L despite maximally tolerated statin therapy (defined as having tried at least two statins, each at least on two reduced doses) for at least 3 months prior to enrolment. Patient outcomes for lipid lowering were assessed at baseline and twice more approximately 4-6 months apart. Physicians were asked to manage their patients as they wished and in addition physician reminders to follow CPG recommendations[2] were provided at each visit; physicians were also asked to provide reason when guidelines were not followed.

2.1 | Statistical Analysis

Continuous data are shown as means with standard deviation and categorical data as frequencies and percentages. Group comparisons were made using the chi-squared test and t test or Kruskal-Wallis test for discrete and continuous variables, respectively, where appropriate. We used repeated measures analysis to perform univariate and multivariable regression to determine the outcome across the visits. While the primary endpoint for GOAL Canada[11] was the proportion of patients achieving the recommended LDL-C level, the purpose of this analysis was a comparison between specialists and PCPs with respect to any differences in the primary endpoint and the use of additional recommended lipid-lowering therapies.

Multivariable logistic regression model was developed to assess factors independently associated with LDL-C achieving target of ≤2.0 mmol. The following variables were considered: variables in Table 1 with $P < .05$ and specialist or PCP group. To account for the clustering of patients within visits, we performed a generalized estimating equations model. The working correlation structure selected was based on its lowest quasi-likelihood under the independence model criterion (QIC). Adjusted odds ratio (OR) with 95% confidence intervals (CI) are presented. A value of $P < .05$ was considered significant for all tests. All statistical analyses were performed in SAS software version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

A total of 177 physicians (102 PCPs and 75 specialists) enrolled 2009 patients; most of the specialists were cardiologists or internists. Ontario contributed more than any other province with the top four being Ontario, BC, Quebec and Alberta. The number of patients

TABLE 1 Clinical baseline characteristics

Variables	PCPs (N = 1006)	Specialists (N = 1003)	*P*
Age, years[a]	62 ± 11	63 ± 11	0.04
Female (%)	398 (40)	447 (45)	0.02
Caucasian/White (%)	652 (65)	774 (77)	0.0001
Private insurance (%)	668 (66)	616 (61)	0.02
Systolic BP (mm Hg)[a]	128 ± 14	130 ± 17	0.004
Diastolic BP (mm Hg)[a]	77 ± 10	77 ± 10	0.76
Heart rate (beats/min)[a]	74 ± 10	71 ± 12	0.0001
BMI (kg/m^2)[a]	29.4 ± 6.7	29.6 ± 6.7	0.57
Coronary artery disease (%)	414 (41)	622 (62)	0.0001
Cerebrovascular disease (%)	89 (9)	76 (8)	0.30
Abdominal aortic aneurysm (%)	17 (2)	21 (2)	0.51
Peripheral arterial disease (%)	86 (9)	97 (10)	0.38
Microvascular disease (%)	49 (5)	39 (4)	0.28
Familial hypercholesterolemia (%)	528 (52)	427 (43)	0.0001
History of smoking (%)	469 (47)	497 (50)	0.19
Diabetes (%)	411 (41)	297 (30)	0.0001
Hypertension (%)	637 (63)	573 (57)	0.005
Chronic kidney disease (%)	102 (10)	61 (6)	0.0009
Atrial fibrillation (%)	55 (6)	86 (9)	0.006
Family history of premature CVD (%)	409 (41)	478 (48)	0.002
Cancer (%)	46 (5)	52 (5)	0.58
Liver disease (%)	29 (3)	12 (1)	0.006
Heart failure (%)	38 (4)	35 (3)	0.73
Total Cholesterol (mmol/L)[a]	5.52 ± 1.37	5.39 ± 1.38	0.03
LDL-C (mmol/L)[a]	3.35 ± 1.25	3.33 ± 1.28	0.69
HDL-C (mmol/L)[a]	1.31 ± 0.42	1.32 ± 0.42	0.70
Non-HDL-C (mmol/L)[a]	4.18 ± 1.45	4.07 ± 1.41	0.10
Triglycerides (mmol/L)[a]	2.18 ± 1.87	1.85 ± 1.22	<0.0001
Statin (%)	804 (80)	731 (73)	0.0002
Ezetimibe (%)	242 (24)	269 (27)	0.15
Bile acid sequestrant (%)	72 (7)	30 (3)	<0.0001
Fibrate (%)	27 (3)	28 (3)	0.88
Niacin (%)	3 (0.3)	5 (0.5)	0.51
Aspirin	519 (52%)	634 (63%)	0.0001
Other antiplatelets	137 (14%)	182 (18%)	0.006
ACE inhibitor	391 (39%)	376 (37%)	0.52
ARB	236 (23%)	214 (21%)	0.25
Beta blocker	303 (30%)	483 (48%)	0.0001
Calcium channel blocker	240 (24%)	209 (21%)	0.10
Diuretic	202 (20%)	179 (18%)	0.20
Oral anticoagulant therapy	58 (6%)	87 (9%)	0.01
ARNI	4 (0.4%)	6 (0.6%)	0.55
Spironolactone/Eplerenone	14 (1%)	20 (2%)	0.30

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index.

[a]Mean ± SD.

enrolled by specialists (n = 1003) and PCPs (n = 1006) was almost equal. There was no difference in the follow-up completion of visit 3 among specialists (80%) and PCPs (75%).

Patients enrolled by specialists were slightly older, more frequently female and Caucasian (77% vs 65%, $P = .0001$) and with other differences in clinical characteristics summarized in Table 1. Specialists had less patients on statin therapy and bile acid sequestrants but more patients on aspirin and other antiplatelet therapies as well as beta blockers (Table 1). Patients treated by specialists had slightly lower total cholesterol and triglycerides but no difference in LDL-C or non-HDL-C levels (Table 1).

At baseline and during the follow-up, the specialists tended to use less statins (Figure 1) but more additional and recommended non-statin therapy (Figure 1). PCPs used more of other, non-guideline recommended lipid-lowering therapies such as niacin or fibrate as compared with specialists (10% vs 6%, $P = .007$).

The mean LDL was 3.3 mmol/L at baseline (visit 1) and decreased significantly to 2.4 and 2.2 mmol/L, respectively, during the follow-up in visits 2 and 3,[11] and there was no difference in the extent of decrease between specialists and PCPs (Figure 2). The proportion of patients achieving the CCS recommended LDL-C level of <2.0 mmol/L (primary endpoint) increased significantly to 41.7% and 50.8% in visits 2 and 3, respectively,[11] and was similar between specialists and PCPs (Figure 3).

Physician responses as to why they were not following guidelines with respect to additional therapy of ezetimibe and/or PCSK9i are summarized in Figure 4; physicians did not provide reasons for not following the guidelines for each patient. The two most frequent reasons provided were patient refusal (more common by specialists) and additional therapy not perceived to be needed. Importantly, both groups of physicians (more often PCPs than specialists) stated that additional therapy would be prescribed at the next visit. Cost, as a reason for not following the guidelines was more commonly sited by PCPs while co-morbidities, patient intolerance or social constraint was more frequently cited by specialists (Figure 4).

Multivariable analysis identified female gender, history of FH and chronic kidney disease as being associated with a lower likelihood of achieving recommended LDL-C level while age, CAD and diabetes as being predictors of achieving the recommended level. Care by a specialist vs. PCP was not significantly associated with achieving the recommended LDL-C level (1.02 [95% CI: 0.87-1.20] $P = .80$). The use of any recommended lipid-lowering therapy was the strongest indicator of achieving LDL-C < 2.0 mmol/L with the odds ratio and 95% CI for statin 3.10 (2.54-3.78, $P < .0001$), ezetimibe 1.71 (1.46-2.01, $P < .0001$) and PCSK9i 17.21 (13.69-21.63, $P < .0001$).

4 | DISCUSSION

Established CVD and FH are both associated with major adverse cardiovascular morbidity and mortality. Aggressive lowering of LDL-C has been shown to reduce the risk of cardiovascular events and mortality in both of these groups.[14-16] Despite the use of high-intensity statin therapy, many patients do not achieve the recommended LDL-C level. The addition of second and third-line therapies has been shown to reduce residual cardiovascular risk.[14-16] Reminders to physicians to adhere to CPG treatment targets was recently shown to result in more patients achieving the recommended LDL-C in both patients with established CVD and FH.[11]

This analysis of the GOAL Canada study[11] compared management by specialists and PCPs with respect to their following of the guidelines recommendations. The proportion of patients enrolled by specialists and PCPs turned out to be very close, a serendipitous outcome, which provided an excellent opportunity for this comparison. No difference in the achievement of the recommended LDL-C level or reduction in the LDL-C during follow-up was seen between the specialist and PCP groups and this finding was further supported on the multivariable analysis.

A number of important care gaps were identified. At baseline, a significant proportion of patients were not treated with any statin therapy which suggests a knowledge gap and physician unfamiliarity with establishing and maintaining statin use while dealing with potential statin intolerance. What was even more surprising is that the proportion of patients not on statin therapy was significantly greater among specialists. One can speculate that perhaps the patients followed by specialists were more likely to have statin tolerability issues. On the other hand, specialists were more likely to use recommended additional therapy such as ezetimibe and/or PCSK9i. However, there was no difference between the specialists and PCP groups in lowering of the LDL-C during follow-up or in the proportion of patients achieving the recommended LDL-C level, despite this greater use. Previous comparisons using administrative database for

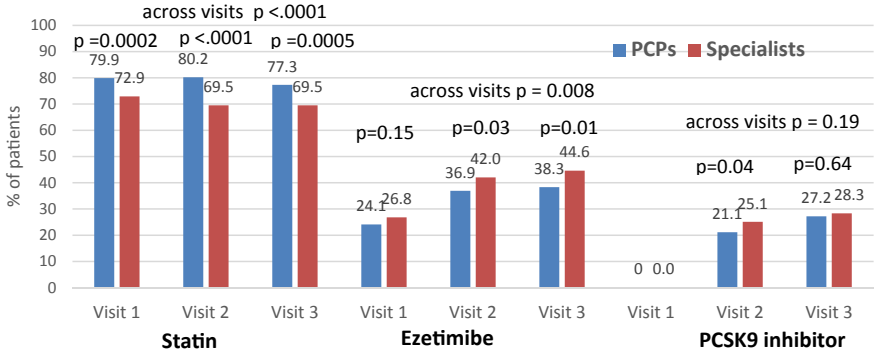

FIGURE 1 The use of ezetimibe and PCSK9 inhibitor at baseline and during follow-up

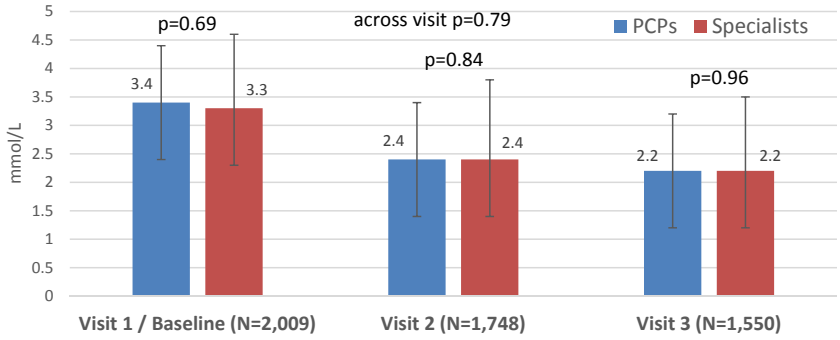

FIGURE 2 Changes in LDL-C with follow-up

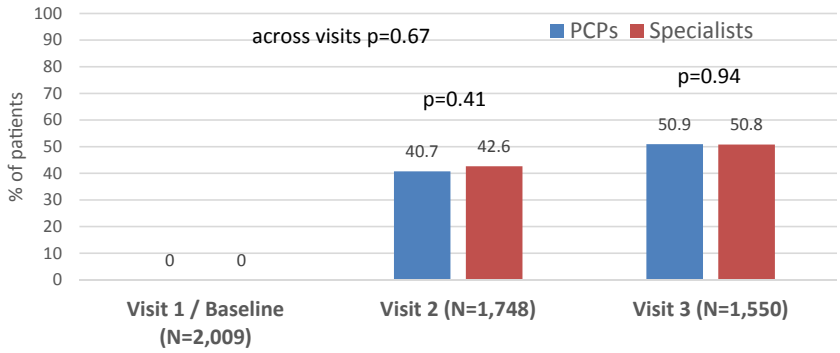

FIGURE 3 Proportion of patients achieving recommended LDL-C level <2 mmol/L

diabetes care, also revealed a care gap of similar proportions between specialist and PCP care.[17]

Additional evidence of a knowledge gap is revealed by physician responses regarding why recommended therapy was not being used. The second most common reason for not following the guidelines was that additional therapy was not needed despite the LDL-C being clearly above the recommended level. This is the clearest example of a knowledge gap or a manifestation of treatment inertia for both groups of physicians and requires additional per-to-peer education. Patient intolerance was the most frequent response by specialists and PCPs and raises a question of how well patients are informed about their personal cost of non-adherence. Given there was no significant difference in this response between PCPs and specialists, strongly suggests how difficult patient non-adherence will be to address.

A response by physicians confirming that additional recommended therapy will be prescribed at the next visit was more frequent with PCPs and is an example of an action gap indicating treatment inertia coupled with a realization that adherence with guidelines improves care. Addressing the challenges that have prevented physicians from optimizing therapy before the reminder is important in closing the care gap.

4.1 | Limitations

This post hoc analysis is subject to physician selection and participation bias; however, if the bias is operative in a similar fashion for PCPs and specialists, our findings are balanced, though not necessarily representative of the overall physician population. Selection bias may have also resulted in the selection of physicians who were interested in cholesterol lowering through their prior participation in similar programs. If this selection bias was present, then our findings of the care gap are even more pronounced indicating treatment inertia even among those more likely to be skilled in the art of LDL-C lowering. The case mix of patients seen may also differ between specialists and PCPs. We believe our findings are inclusive of this potential difference and represent each group of physicians accordingly.

5 | CONCLUSION

Specialists and PCPs have a complimentary role to play in the management of patients with cardiovascular disease with respect to lipid-lowering therapy and both groups exhibit similar treatment inertia. Important knowledge and action care gaps require additional education and support systems, respectively, in order to optimize care and overcome barriers contributing to optimal care.

DISCLOSURE

AL has received on behalf of the Canadian Heart Research Centre research grant support from Actelion, Amgen, Bayer, BMS, Merck, Novo Nordisk, Pfizer, Servier and Sanofi. GBJM has received grants and/or honoraria from Amgen, Sanofi, HLS Therapeutices, Esperion, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen/Johnson & Johnson, Novartis, Novo Nordisk. LAL has received research grant support from Astra Zeneca, Amgen, Kowa, The Medicines Company and Sanofi. He

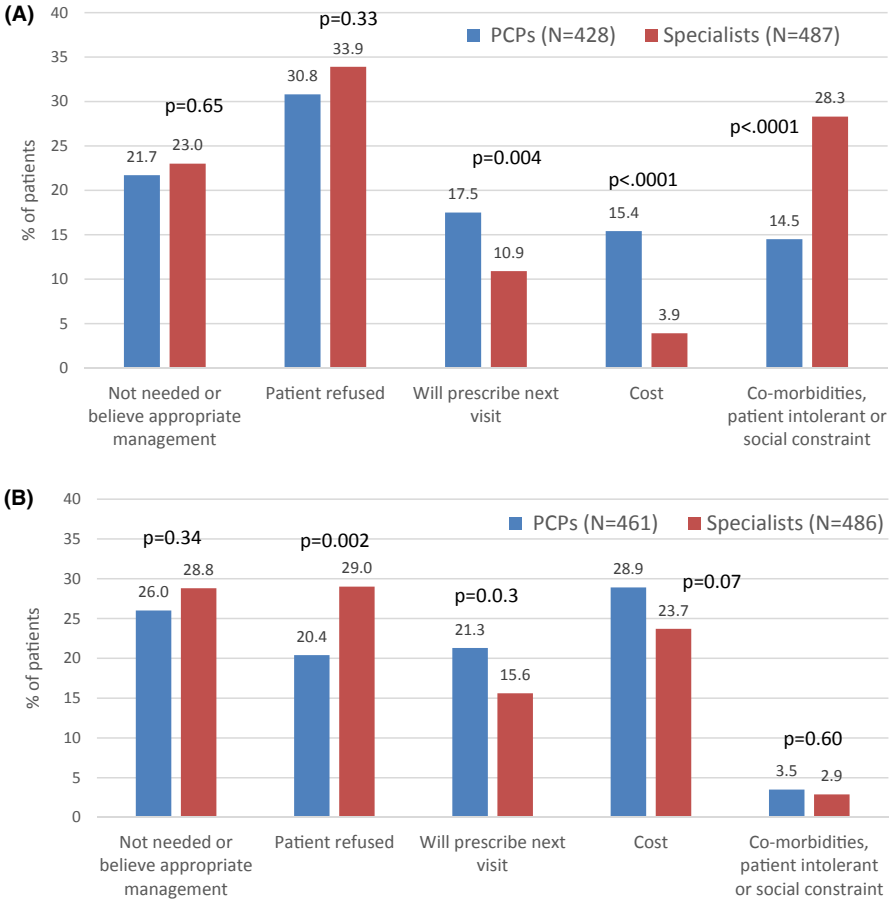

FIGURE 4 Reasons for not following the recommended therapy

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